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Crit Care Clin 21 (2005) 329–346

CRITICAL
CARE
CLINICS

Determinants of Plasma Acid-Base Balance

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Acid-base abnormalities are extremely common in modern ICUs. Although most cases are mild and self-limiting, there are certain circumstances in which acid-base derangements are dangerous. Such is the case when the disorders are extreme (eg, pH <7.0 or >7.7); especially when the acid-base derangement develops quickly. Such severe abnormalities can be the direct cause of organ dysfunction. Clinical manifestations can include cerebral edema, seizures, decreased myocardial contractility, pulmonary vasoconstriction, and systemic vasodilation to name a few. Furthermore, even less extreme derangements may produce harm because of the patient's response to the abnormality. For example, a spontaneously breathing patient who has metabolic acidosis attempts to compensate by increasing minute ventilation. The workload that is imposed by increasing minute ventilation can lead to respiratory muscle fatigue with respiratory failure or diversion of blood flow from vital organs to the respiratory muscles which results in organ injury. Acidemia is associated with increased adrenergic tone and, on this basis, can promote the development of cardiac dysrhythmias in critically ill patients, or increase myocardial oxygen demand in patients who have myocardial ischemia. In such cases, it may be prudent to treat the underlying disorder and to provide symptomatic treatment for the acid-base disorder. Accordingly, it is important to understand the causes of acid-base disorders and the limitations of various treatment strategies. Finally, emerging evidence suggests that changes in acid-base variables influence immune effector cell function [1,2]. Thus, avoiding acid-base derangements may prove to be important in the management of critically ill patients for their own sake and

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0749-0704/05/$ – see front matter
doi:10.1016/j.ccc.2005.01.010 *criticalcare.theclinics.com*

for the sake of standardizing study protocols that attempt to manipulate immunologic responses (eg, anticytokine therapies).

Classification and quantification of acid-base disorders

To diagnose, treat, and it is hoped that, to avoid acid-base disorders it is paramount that the critical care clinician recognize acid-base disturbances and understand how and why they occur. To understand acid-base physiology it is important to agree on how to describe and measure it. Since Sörensen first introduced the pH notation, we have used the pH scale to quantify acid-base balance. The pH scale has a tremendous advantage because it lends itself to colorimetric and electrometric techniques. There also is some physiologic relevance to the logarithmic pH scale [3]. pH is a confusing variable, however. It is a nonlinear transformation of H^+ concentration—the logarithm of its reciprocal. Strictly speaking, pH only can be thought of as a dimensionless representation of H^+ concentration and is not, itself, a concentration. pH actually is the logarithmic measure of the volume that is required to contain 1 Eq of H^+. In blood plasma at pH 7.4, this volume is roughly 25 million liters [4].

Regardless of how we express the concentration of H^+, either directly or as the pH, it generally is accepted that changes in blood H^+ concentration occur as the result of changes in volatile (P_{CO_2}) and nonvolatile acids (eg, hydrochloric, sulfuric, lactic). Clinically, changes in volatile acid are referred to as ''respiratory'' and changes in nonvolatile acids are referred to as ''metabolic.'' There are three major methods of quantifying (describing) acid-base disorders; each differs only in assessment of this latter, ''metabolic'' component. These three methods quantify the metabolic component by using (1) HCO_3^- (in the context of P_{CO_2}); (2) the standard base excess (SBE); or (3) the strong ion difference (SID). Although there has been significant debate about the accuracy and usefulness of each method compared with the others, all three yield virtually identical results when used to quantify the acid-base status of a given blood sample [5,6]. The only differences between these three approaches are conceptual (ie, in how they approach the understanding of the mechanism) [7–9].

Beyond Henderson and Hasselbalch

Since Hasselbalch adapted the Henderson equation to the pH notation of Sörensen, the following equation has been used to understand the relationship between respiratory and metabolic acid-base variables:

$$pH = pK \times \log\left[HCO_3^- / (0.03 \times P_{CO_2})\right]$$

This is the Henderson-Hasselbalch (HH) equation and it is important to realize what this equation tells us. An increase in P_{CO_2} will result in a decrease in pH

and an increase in HCO_3^- concentration. Thus, a patient who has a low blood pH—a condition that is known as acidemia—will have an increased P_{CO_2} or a P_{CO_2} that is "not increased." In the former circumstance, we classify the disorder as a "respiratory acidosis". We use the term "acidosis" to describe the process that results in acidemia, and "respiratory" because the apparent cause is an increased P_{CO_2}. This is logical because carbonic acid results when CO_2 is added to water (or blood) and the resultant decrease in pH is entirely expected. In the latter condition, P_{CO_2} is not increased, and thus, there cannot be a respiratory acidosis. Therefore, we refer to this condition as "metabolic" because some nonvolatile acid must be the cause of the acidemia. We can reverse the above logic and easily classify simple conditions of alkalemia as resulting from respiratory or metabolic alkaloses. Thus, the HH equation allows us to classify disorders as to the primary type of acid that is being increased or decreased. Over time, physiology superimposes its effects on simple chemistry and the relationship between P_{CO_2} and HCO_3^- is altered to reduce the alterations in pH. By carefully examining the changes that occur in P_{CO_2} and HCO_3^- in relationship to each, however, one can discern highly conserved patterns. In this way, rules can be established to allow one to discover mixed disorders and to separate chronic from acute respiratory derangements. For example, one such rule is the convenient formula [10] for predicting the expected P_{CO_2} in the setting of a metabolic acidosis:

$$P_{CO_2} = \left(1.5 \times HCO_3^-\right) + 8 \pm 5$$

This rule tells that the P_{CO_2} should be secondary to the increase in alveolar ventilation that accompanies a metabolic acidosis. If P_{CO_2} does not change enough or changes too much, we classify the condition as a "mixed" disorder, with a respiratory acidosis if the P_{CO_2} remains too high or a respiratory alkalosis

Table 1
Observational acid-base patterns

Disorder	HCO_3^- (mEq/L)	P_{CO_2} (mm Hg)	SBE (mEq/L)
Metabolic acidosis	<22	$= (1.5 \times HCO_3^-) + 8$ $= 40 + SBE$	<−5
Metabolic alkalosis	>26	$= (0.7 \times HCO_3^-) + 21$ $= 40 + (0.6 \times SBE)$	>+5
Acute respiratory acidosis	$= [(P_{CO_2} - 40)/10] + 24$	>45	= 0
Chronic respiratory acidosis	$= [(P_{CO_2} - 40)/3] + 24$	>45	$= 0.4 \times (P_{CO_2} - 40)$
Acute respiratory alkalosis	$= [(40 - P_{CO_2})/5] + 24$	<35	= 0
Chronic respiratory alkalosis	$= [(40 - P_{CO_2})/2] + 24$	<35	$= 0.4 \times (P_{CO_2} - 40)$

Data from Kellum JA. Determinants of blood pH in health and disease. Crit Care 2000;4:6–14.

if the change is too great. This rule, along with others (Table 1) recently was translated to SBE terminology [6]:

$$P_{CO_2} = (40 + SBE) \pm 5$$

For example, consider the following arterial blood gas sample: pH 7.31, P_{CO_2} 31, HCO_3^- 15, SBE −9.5. The first formula tells us that the expected $P_{CO_2} = (1.5 \times 15) + 8 = 30.5 \pm 5$ and the SBE added to 40 also yields 30.5. The measured P_{CO_2} of 31 mm Hg is consistent with a pure metabolic acidosis (ie, no respiratory disorder).

It is equally important to understand what the HH equation does not tell us. First, it does not allow us to discern the severity (quantity) of the metabolic derangement in a manner analogous to the respiratory component. For example, when there is a respiratory acidosis, the increase in the P_{CO_2} quantifies the derangement, even when there is a mixed disorder. The metabolic component only can be approximated by the change in HCO_3^-, however. Further, relying on the change in HCO_3^- is potentially misleading and is the primary reason why inexperienced clinicians find acid-base balance confusing. Consider the following arterial blood gas measurements.

A. pH 7.19, P_{CO_2} 40, HCO_3^- 15
B. pH 7.55, P_{CO_2} 18, HCO_3^- 15
C. pH 7.10, P_{CO_2} 74, HCO_3^- 22

Blood gases A and B have exactly the same value for HCO_3^-, yet when 7.40 is used as the reference point, there is twice the titratable acid in sample A compared with sample B. Furthermore C has the same amount of metabolic acidosis as B, yet the HCO_3^- concentration is considerably higher. This is no surprise to the trained observer. The higher pH in sample B belies the ''lesser'' acidosis—but how much less? It is impossible to tell by simply looking at the HCO_3^-.

Second, the HH equation does not tell us about any acids other than carbonic acid. The relationship between CO_2 and HCO_3^- provides a useful clinical ''road map'' to guide the clinician in uncovering the etiology of an acid-base disorder as described above. The total CO_2 concentration, however, and hence, the HCO_3^- concentration, is determined by the P_{CO_2}, which, in turn, is determined by the balance between alveolar ventilation and CO_2 production. HCO_3^- cannot be regulated independent of P_{CO_2}. The HCO_3^- concentration in the plasma always increases as the P_{CO_2} increases, yet this is not an alkalosis. To understand how the pH and HCO_3^- concentration are altered independent of P_{CO_2}, we must look beyond Henderson and Hasselbalch.

Base excess

To address the first ''shortcoming'' of the HH equation—the inability to quantify the metabolic component—several methods have been devised. In 1948,

Singer and Hastings [11] proposed the term "buffer base" (BB) to define the sum of HCO_3^- plus the nonvolatile weak acid buffers (A^-). A change in BB corresponds to a change in the metabolic component. The methods for calculating the change in BB were refined by investigators [12,13] and refined further by others [14,15] to yield the base excess (BE) methodology. BE is the quantity of metabolic acidosis or alkalosis that is defined as the amount of acid or base that must be added to a sample of whole blood in vitro to restore the pH of the sample to 7.40 while the P_{CO_2} is held at 40 mm Hg [13]. Although this calculation is accurate in vitro, inaccuracy exists when applied in vivo because BE changes with changes in Pco2 [16,17]. This effect is understood to be due to equilibration across the entire extracellular fluid space (whole blood plus interstitial fluid). When the BE equation is modified to account for an "average" content of hemoglobin across this entire space, a value of 5 g/dL is used instead; this defines the SBE. This value does not represent the true content of hemoglobin that is suspended in the volume of whole blood together with interstitial fluid, but rather is an empiric estimate that improves the accuracy of the BE. It can be argued that the entire extracellular fluid space is involved in acid-base balance because this fluid flows through blood vessels and lymphatics and mixes constantly [18]. Thus, the value of SBE is that it quantifies the change in metabolic acid-base status in vivo. BE is only accurate in vivo when it assumes a constant hemoglobin concentration.

The BE approach does not address the second problem that is associated with using the HH equation alone, (ie, it does not tell us about the mechanisms of metabolic acid-base balance). For example the body does not "regulate" the SBE. It is not a substance that can be excreted in the feces or reabsorbed from the proximal tubule. Similarly, HCO_3^- is not a strong acid or base; its addition to, or removal from, the plasma cannot be translated into changes in SBE. This is not to say that changes in SBE and HCO_3^- do not correlate closely, for they do. Correlation and causation are not the same thing. Traditionally, the difference has been ascribed to the effects of "buffering," the argument being that strong acid (or base), quantified by SBE, is "buffered" by plasma proteins, hemoglobin, HCO_3^-, and even bone. The resulting changes in HCO_3^- and pH are a result of this buffering process. As explained by Stewart [4,7] and confirmed experimentally by others [19,20], the fundamental physical-chemical properties of biologic solutions dictate much of this so-called "buffering."

Physical-chemical properties of biologic solutions

A physical-chemical analysis of acid-base physiology requires the application of two basic principles. The first is electroneutrality, which dictates that in aqueous solutions, the sum of all positively-charged ions must equal the sum of all negatively-charged ions. The second is conservation of mass, which means that the amount of a substance remains constant unless it is added or generated, or removed or destroyed. These principles may seem basic, but they often are over-

looked in the analysis of clinical acid-base physiology and lead to incorrect conclusions. For example, a hyperchloremic metabolic acidosis can be brought about in only two ways. First, Cl^- ions can be added to the circulation, either by way of an exogenous source (eg, HCl or saline) or internal shifts (eg, from the red cell). Second, Cl^- ions can be retained or reabsorbed while water and other ions (eg, Na^+) are excreted, so that the relative concentration of Cl^- increases. A decrease in HCO_3^- or H^+ concentration does not produce hyperchloremia; hyperchloremia is a cause of acidosis. This distinction is not merely semantics—any more than Copernicus' observation that the Earth, rather than the sun, moves [9,21].

In addition to these physical-chemical principles, almost all solutions of biologic interest share two important characteristics. Virtually all are aqueous (composed of water) and most are alkaline (OH^- concentration greater than H^+ concentration). Because these characteristics are so universal in human physiology, they often are ignored in reviews of physiology, especially for clinical medicine. Yet, they are extremely important. Aqueous solutions contain a virtually inexhaustible source of H^+. Although pure water dissociates only slightly into H^+ and OH^-, electrolytes and CO_2 produce powerful electrochemical forces that influence water dissociation. Similarly, aqueous solutions that are alkaline behave differently, compared with acidic solutions, in terms of the extent to which changes in their composition influence changes in pH.

To illustrate this point, first consider a 1-liter solution of pure water. Pure water contains only a small amount of H^+ and OH^- ions and molecular H_2O. Pure water is a neutral solution by definition because the H^+ and OH^- concentrations are equal. The concentration of these ions is determined solely by the extent to which water dissociates and can be defined by a constant, K'_w. Water dissociation is temperature sensitive because K'_w is, but, at all times, the concentrations of H^+ and OH^- must be equal, and $H^+ \times OH^- = K'_w$. If we add 10 mEq each of Na^+ and Cl^- to this 1-liter solution of pure water, we have an aqueous solution that contains H^+, OH^-, Na^+, and Cl^- ions and molecular water. The solution does not contain any molecules of NaOH, HCl, or NaCl because Na^+ and Cl^- are strong ions and as such, are dissociated completely in water. The solution is still a neutral solution by definition and at 25°C, the concentrations of H^+ and OH^- are approximately 100 nEq/L, or pH 7.0. If we add 10 mEq/L of HCl, we have a solution that contains 10 mEq/L of Na^+ and 20 mEq/L of Cl^-. This solution is acidic: $OH^- = 4.4 \times 10^{-9}$ nEq/L and H^+ = approximately 10 mEq/L. In this acidic solution, the H^+ concentration increased by the amount of H^+ added (ie, 10 mEq/L). If instead of HCl we were to add 10 mEq/L of NaOH, the solution would contain 20 mEq/L of Na^+ and 10 mEq/L of Cl^- and would be alkaline: $H^+ = 4.4 \times 10^{-9}$ nEq/L and OH^- = approximately 10 mEq/L. If we add 5 mEq/L of HCl to this alkaline solution, the resulting concentration of Na^+ would be 20 mEq/L and Cl^- would be 15 mEq/L. The final H^+ concentration is now 8.8×10^{-9} nEq/L and OH^- is approximately 5 mEq/L. In this final example, 5 mEq of H^+ were added to the solution, yet the final concentration of free H^+ changed by less than one billionth of this amount. It

also should be noted that the solution contains no "buffers"; thus, what often is attributed to the power of buffering systems is merely a physical-chemical property of alkaline solutions.

Determinants of H^+ concentration

From the preceding discussion it is apparent that, for aqueous solutions, water is the primary source of H^+ and the determinants of H^+ concentration are the determinants of water dissociation. Even for an aqueous solution that is as complex as blood plasma, only three independent variables determine H^+ concentration. The author uses the term "determine," rather than "describe" because, as shown by Stewart [4,7], these three variables are mathematically independent determinants of the H^+ concentration. Thus, these variables are related causally to the H^+ concentration, rather than merely being correlated. The distinction between independent and dependent, and between causation and correlation, is as important to acid-base physiology as any other area of science. Only by the careful analysis of causal variables can mechanisms be determined. For blood plasma, these three variables are P_{CO_2}, SID, and the total weak acid concentration (A_{TOT}).

Carbon dioxide

CO_2 is an independent determinant of pH and is produced by cellular metabolism or by the titration of HCO_3^- by metabolic acids. Normally, alveolar ventilation is adjusted to maintain the arterial P_{CO_2} between 35 mm Hg and 45 mm Hg. When alveolar ventilation is increased or decreased out of proportion to P_{CO_2} production, a respiratory acid-base disorder exists. CO_2 production by the body (at 220 mL/min) is equal to 15,000 mmol/d of carbonic acid [22]. This compares to less than 500 mmol/d for all nonrespiratory acids. The respiratory center, in response to signals from P_{CO_2}, pH, and P_{O_2}, as well as some from exercise, anxiety, wakefulness, and others, controls alveolar ventilation. A precise match of alveolar ventilation to metabolic CO_2 production maintains the normal arterial P_{CO_2} of 40 mm Hg. Arterial P_{CO_2} is adjusted by the respiratory center in response to altered arterial pH that is produced by metabolic acidosis or alkalosis in predictable ways (see Table 1).

When CO_2 elimination is inadequate relative to the rate of tissue production, P_{CO_2} increases to a new steady state that is determined by the new relationship between alveolar ventilation and CO_2 production. Acutely, this increase in P_{CO_2} increases the H^+ and the HCO_3^- concentrations according to the HH equation. Thus, this change in HCO_3^- concentration is mediated by chemical equilibrium, not by any systemic adaptation. Similarly, this increased HCO_3^- concentration does not "buffer" H^+ concentration. There is no change in the SBE. Tissue

acidosis always occurs in respiratory acidosis because CO_2 diffuses into the tissues. If the P_{CO_2} remains increased, the body attempts to compensate by altering another independent determinant of pH, namely the SID.

Electrolytes (strong ions)

Blood plasma contains numerous ions. These ions can be classified by charge—positive "cations" and negative "anions"—as well as by their tendency to dissociate in aqueous solutions. Some ions are dissociated completely in water (eg, Na^+, K^+, Ca^{++}, Mg^{++}, and Cl^-. These ions are called "strong ions" to distinguish them from "weak ions" (eg, albumin, phosphate, HCO_3^-), which can exist as charged (dissociated) and uncharged forms. Certain ions, such as lactate, are dissociated so nearly completely that they may be considered strong ions under physiologic conditions. In a neutral salt solution that contains only water and NaCl, the sum of strong cations (Na^+) minus the sum of strong anions (Cl^-) is zero, (ie, $Na^+ = Cl^-$). In blood plasma, however, strong cations (mainly Na^+) outnumber strong anions (mainly Cl^-). The difference between the sum of all strong cations and all strong anions is known as the SID. SID has a powerful electrochemical effect on water dissociation, and hence, on H^+ concentration. As SID becomes more positive, H^+, a "weak" cation decreases (and pH increases) to maintain electrical neutrality (Fig. 1).

In healthy humans, the plasma SID is between 40 mEq/L and 42 mEq/L, although it often is different in critically ill patients. According to the principle of electrical neutrality, blood plasma cannot be charged; the remaining negative charges that balance the SID come from CO_2 and the weak acids (A^-) and, to a small extent, from OH^-. At physiologic pH, the contribution of OH^- is so small

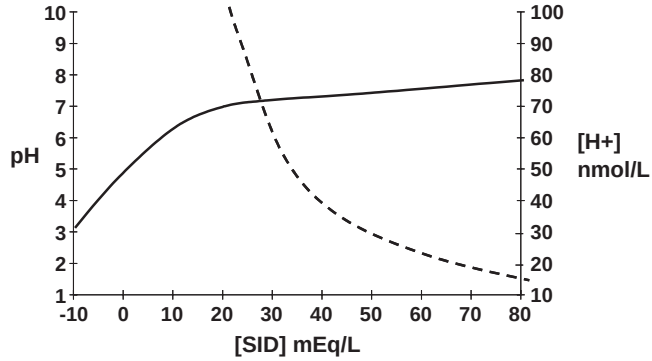

Fig. 1. Plots of pH (—) and H^+ (----) versus strong ion difference (SID). For these plots, A_{TOT} and P_{CO_2} were held constant at 18 mEq/L and 40 mm Hg, respectively. Assumes a water dissociation constant for blood of 4.4×10^{-14} (Eq/L). Note how steep the pH curve becomes at SID of less than 20 mEq/L.

(nEq range) that it can be ignored. The A_{TOT} (mainly albumin and phosphate) can be considered together and $AH + A^- = A_{TOT}$. The SID of a blood sample can be estimated from the value of the remaining negative charge because $SID - (CO_2 + A^-) = 0$. This estimate of SID has been termed the "effective SID" (SIDe) [23], but it really is no different from the BB that was described more than 50 years ago [11]. Thus, SID and BB are mirror images of each other. Recall that SBE essentially is the change in BB in vivo, and hence, SBE defines the change in SID from the equilibrium point where pH = 7.4 and P_{CO_2} = 40 mm Hg [5].

An alternative estimate of SID is:

$$(Na^+ + K^+ + Ca^{++} + Mg^{++}) - (Cl^- + \text{lactate}^-)$$

This often is referred to as the "apparent" SID (SIDa), with the understanding that some "unmeasured" ions also may be present [23]. Neither SIDe nor SIDa is a perfect estimate of the true SID. Blood samples from patients may contain unmeasured strong ions (eg, sulfate, ketones) that make SIDa an inaccurate estimate of SID. Similarly, these patients may have abnormal weak ions (eg, proteins) that make the SIDe inaccurate. In healthy humans, however, SIDa and SIDe are nearly identical, and thus, are valid estimates of SID [23]. Furthermore, when SIDa and SIDe are not equal—a condition that is referred to as the strong ion gap (SIG), where SIDa − SIDe = SIG—abnormal strong or weak ions must be present [24]. The SIG is positive when unmeasured anions are greater than unmeasured cations and negative when unmeasured cations are greater than unmeasured anions. Unexplained anions, and in some cases, cations, have been found in the circulation of patients who had a variety of diseases [24–27] and in animals under experimental conditions [28].

The SIG is not the same as the anion gap (AG). Normally, the SIG is near zero, whereas the AG is 8 mEq/L to 12 mEq/L. The AG is an estimate of the sum of $SIG + A^-$. Thus, subtracting A^- from the AG approximates the SIG. A convenient and reasonably accurate way to estimate A^- is to use the following formula [29]:

$$2(\text{albumin g/dL}) + 0.5(\text{phosphate mg/dL})$$

Or for international units:

$$0.2(\text{albumin g/L}) + 1.5(\text{phosphate mmol/L})$$

The "normal" AG for a person with no unmeasured anions or cations in their plasma is equal to A^-, such that $AG - A^- = SIG = 0$. This technique allows one to "calibrate" the AG for patients who have abnormal albumin or phosphate concentrations.

Physiologic mechanisms that control strong ion difference

To alter the SID, the body must affect a change in the relative concentrations of strong cations and strong anions. The kidney is the primary organ that affects this change. The kidney can excrete only a small amount of strong ion into the urine each minute; therefore, several minutes to hours are required to impact the SID significantly. The handling of strong ions by the kidney is extremely important because every Cl^- ion that is filtered, but not reabsorbed, decreases the SID. Because most of the human diet contains similar ratios of strong cations to strong anions, there usually is sufficient Cl^- available for this to be the primary regulating mechanism. This is particularly apparent when we consider that renal Na^+ and K^+ handling are influenced by other priorities (eg, intravascular volume and plasma K^+ homeostasis). Accordingly, "acid handling" by the kidney generally is mediated through Cl^- balance. How the kidney handles Cl^- is important. Traditional approaches to this problem have focused on H^+ excretion and emphasized the importance of NH_3 and its add-on cation, NH_4^+. H^+ excretion, per se, is irrelevant because water provides an essentially infinite source of H^+. The kidney does not excrete H^+ any more as NH_4^+ than it does as H_20. The purpose of renal ammoniagenesis is to allow the excretion of Cl^- without Na^+ or K^+. This is achieved by supplying a weak cation (NH_4^+) to excrete with Cl^-.

Thus, NH_4^+ is not important to systemic acid-base balance because of its carriage of H^+ or because of its direct action in the plasma (normal plasma NH_4^+ concentration is <0.01 mEq/L), but rather because of its "coexcretion" with Cl^-. NH_4^+ is not produced solely in the kidney. Hepatic ammoniagenesis (and glutaminogenesis) is important for systemic acid-base balance and, as expected, is controlled tightly by mechanisms that are sensitive to plasma pH [30]. This reinterpretation of the role of NH_4^+ in acid-base balance is supported by the evidence that hepatic glutaminogenesis is stimulated by acidosis [31]. Nitrogen metabolism by the liver can result in urea, glutamine, or NH_4^+. Normally, the liver releases only a small amount NH_4^+; it incorporates most of this nitrogen into urea or glutamine. Hepatocytes have enzymes that enable them to produce either of these end-products and both allow for the regulation of plasma NH_4^+ at suitably low levels. The production of urea or glutamine has significantly different effects at the level of the kidney, however. This is because glutamine is used by the kidney to generate NH_4^+ and to facilitate the excretion of Cl^-. Thus, the production of glutamine can be seen as having an alkalinizing effect on plasma pH because of the way in which it is used by the kidney.

Further support for this scenario comes from the recent discovery of an anatomic organization of hepatocytes according to their enzymatic content [32]. Hepatocytes with a propensity to produce urea are positioned closer to the portal venule, and thus, have the first chance at the NH_4^+ that is delivered. Acidosis inhibits ureagenesis, however, and under these conditions, more NH_4^+ is available for the downstream hepatocytes that are predisposed to produce glutamine. Thus, the leftover NH_4^+ is "packaged" as glutamine for export to the kidney where it is used to facilitate Cl^- excretion, and hence, increases the SID.

The gastrointestinal (GI) tract also has important effects on the SID. Along its length, the GI tract handles strong ions differently. In the stomach, Cl^- is pumped out of the plasma and into the lumen which reduces the SID of the gastric juice and the pH. On the plasma side, SID is increased by the loss of Cl^- and the pH is increased; this produces the so-called ''alkaline tide'' that occurs at the beginning of a meal when gastric acid secretion is maximal [33]. In the duodenum, Cl^- is reabsorbed and the plasma pH is restored. Normally, only slight changes in plasma pH are evident because Cl^- is returned to the circulation almost as soon as it is removed. If gastric secretions are removed from the patient, either by suction catheter or vomiting, Cl^- is lost progressively and the SID increases steadily. The Cl^- loss, not the H^+ loss, is the determinant of plasma pH. Although H^+ is ''lost'' as HCl, it also is lost with every molecule of water that is removed from the body. When Cl^- (a strong anion) is lost without the loss of a strong cation, the SID is increased, and therefore, the plasma H^+ concentration is decreased. When H^+ is ''lost'' as water, rather than as HCl, there is no change in the SID, and hence, no change in the plasma H^+ concentration.

In contrast to the stomach, the pancreas secretes fluid into the small intestine that has a SID that is much higher than plasma and is low in Cl^-. Thus, the plasma that perfuses the pancreas has its SID decreased, a phenomenon that peaks approximately an hour after a meal and helps to counteract the alkaline tide. If large amounts of pancreatic fluid are lost (eg, from surgical drainage), acidosis results as a consequence of the decreased plasma SID. In the large intestine, fluid also has a high SID because most of the Cl^- has been removed in the small intestine and the remaining electrolytes primarily are Na^+ and K^+. The body normally reabsorbs much of the water and electrolytes from this fluid but when severe diarrhea exists, large amounts of cations can be lost. If this loss is persistent, the plasma SID decreases and acidosis results. Finally, whether the GI tract is capable of regulating strong ion uptake in a compensatory fashion has not been well-studied. There is some evidence that the gut may modulate systemic acidosis in experimental endotoxemia by removing anions from the plasma [5]; however, the full capacity of this organ to affect acid-base balance is unknown.

Pathophysiologic mechanisms that are responsible for alterations in strong ion difference

Metabolic acidoses and alkaloses are categorized according to the ions that are responsible (eg, lactic acidosis, chloride responsive alkalosis). It is important to recognize that metabolic acidosis is produced by a decrease in the SID; this produces an electrochemical force that results in an increase in free H^+ concentration. A decrease in SID may be brought about by the generation of organic anions (eg, lactate, ketones), the loss of cations (eg, diarrhea), the mishandling of ions (eg, renal tubular acidosis), or the addition of exogenous anions (eg, iatrogenic acidosis, poisonings). By contrast, metabolic alkaloses occur as a result of an inappropriately large SID, although the SID need not be greater

Box 1. Differential diagnosis for metabolic acidosis (decreased strong ion difference)

Renal tubular acidosis

Urine SID (Na + K − Cl) > 0
- Distal (type I): urine pH >5.5
- Proximal (type II): urine pH <5.5/low serum K
- Aldosterone deficiency (type IV): urine pH <5.5/high serum K

Nonrenal

Urine SID (Na + K − Cl) < 0
- Gastrointestinal: diarrhea, small bowel/pancreatic drainage
- Iatrogenic: parenteral nutrition, saline

than "normal" (40–42 mEq/L). This may be brought about by the loss of anions in excess of cations (eg, vomiting, diuretics), or rarely, by administration of strong cations in excess of strong anions (eg, transfusion of large volumes of banked blood). Boxes 1 and 2 provide a useful means of differentiating the various causes of metabolic acidosis and alkalosis.

In the ICU, acidosis usually is more of a problem than alkalosis; in the critically ill, the most common sources of metabolic acidosis are disorders of chloride homeostasis, lactate, and other anions. Hyperchloremic metabolic acidosis occurs as a result of chloride administration or secondary to abnormalities in chloride handling or is related to movements of chloride from one compartment to another. The effect of chloride administration on the development of metabolic acidosis has been known for many years [34,35]. Recently, new attention has been paid to this area in light of the better understanding of the mechanisms that are responsible for this effect [20,36–39]. It was shown in animal models of sepsis [36] and in patients who underwent surgery [37–39] that saline causes metabolic acidosis not by "diluting" HCO_3^-, but rather by its chloride content. From a physical-chemical perspective this is completely expected. HCO_3^- is a dependent variable and cannot be the cause of the acidosis. Instead, Cl^- administration decreases the SID (an independent variable) and produces an increase in water dissociation, and hence, H^+ concentration. The reason why this occurs with saline administration is that although saline contains equal amounts of Na^+ and Cl^-, the plasma does not. When large amounts of salt are added, the Cl^- concentration increases much more than the sodium concentration. For example, 0.9% ("normal") saline contains 154 mEq/L of Na^+ and Cl^-. Administration of large volumes of this fluid will have a proportionally greater effect on total body Cl^- than on total body Na^+. The total body concentrations of these strong ions must be considered; although the true volume of

Box 2. Differential diagnosis of a metabolic alkalosis (increased strong ion difference)

Chloride loss less than sodium loss

- Chloride responsive (urine Cl^- concentration <10 mmol/L)
  - Gastrointestinal losses
    - Vomiting
    - Gastric drainage
    - Chloride wasting diarrhea (villous adenoma)
  - Postdiuretic use
  - Posthypercapnia
- Chloride unresponsive (urine Cl^- concentration >20 mmol/L)
  - Mineralocorticoid excess
    - Primary hyperaldosteronism (Conn's syndrome)
    - Secondary hyperaldosteronism
    - Cushing's syndrome
    - Liddle's syndrome
    - Bartter's syndrome
    - Exogenous corticoids
    - Excessive licorice intake
  - Ongoing diuretic use

Exogenous sodium load (>chloride)

- Sodium salt administration (acetate, citrate)
  - Massive blood transfusions
  - Parenteral nutrition
  - Plasma volume expanders
  - Sodium lactate (ringer's solution)

Other

- Severe deficiency of intracellular cations
  - Magnesium
  - Potassium

distribution of Cl^- is less, like Na^+, the effective volume of distribution (after some time of equilibration) is equal to total body water [19].

There are other important causes of hyperchloremia (see Box 1) and in addition, this form of metabolic acidosis is common in critical illness, especially sepsis. Although saline resuscitation undoubtedly plays a role, there seems to be unexplained sources of Cl^-, at least in animal models of sepsis [19]. We hypothesized that this Cl^- is coming from intracellular and interstitial compart-

ments as a result of the partial loss of Donnan equilibrium that is caused by albumin exiting the intravascular space; however, this hypothesis is unproven.

Weak acids

The third and final determinant of H^+ concentration is the A_{TOT}. The weak acids are mostly proteins (predominantly albumin) and phosphates, and they contribute the remaining charges to satisfy the principle of electroneutrality, such that $SID - (CO_2 + A^-) = 0$. A^- is not an independent variable because it changes with alterations in SID and PCO_2. Rather, A_{TOT} ($AH + A^-$) is the independent variable because its value is not determined by any other. The identification of A_{TOT} as the third independent acid-base variable led some investigators to suggest that a third "kind" of acid-base disorder exists [40]. Thus, along with respiratory and metabolic, there also would be acidosis and alkalosis that are due to abnormalities in A_{TOT}. Mathematical, and therefore, chemical independence does not necessarily imply physiologic independence, however. Although the loss of weak acid (A_{TOT}) from the plasma space is an alkalinizing process [20], there is no evidence that the body regulates A_{TOT} to maintain acid-base balance. Furthermore, there is no evidence that clinicians should treat hypoalbuminemia as an acid-base disorder.

Critically ill patients frequently have hypoalbuminemia, and as such, their A_{TOT} is reduced; however, these patients often are alkalemic and their SID also is reduced [41]. When these patients have a normal pH and a normal SBE and HCO_3^- concentration, it seems most appropriate to consider this to be physiologic compensation for a decreased A_{TOT} [42], rather than classifying this condition as a complex acid-base disorder with a mixed metabolic acidosis/hypoalbuminemic alkalosis. Thus, it seems far more likely that this "disorder" is the normal physiologic response to a decreased A_{TOT}. Furthermore, because changes in A_{TOT} generally occur slowly, the development of alkalemia requires the kidney to continue to excrete Cl^-, despite an evolving alkalosis. The author considers such a scenario to be renal-mediated hypochloremic metabolic alkalosis, the treatment for which includes fluids or chloride, depending on the clinical conditions. Stewart's [4] designation of a "normal" SID of approximately 40 mEq/L was based on a "normal" CO2 and A_{TOT}. The "normal" SID for a patient who has an albumin of 2 g/dL would be much lower (eg, ~32 mEq/L).

Unexplained anions

In addition to Cl^-, several other anions may be present in the blood of critically ill patients. Lactate may be the most important of these, but ketones, sulfates, and certain poisons (eg, methanol, salicylate) are important in the appropriate clinical conditions. In addition, unexplained anions were shown to be present in the blood of many critically ill patients [24–27]. It is important to emphasize that strong and weak ions alter the SIG (and the anion gap). Thus, the

exact chemical makeup of the SIG may vary significantly from patient to patient. Healthy humans and laboratory animals seem to have little, if any, unmeasured anions, so their SIG is near zero. One study that cited a previously published laboratory dataset calculated the total unmeasured anions in the blood of exercising humans to be 0.3 mEq/L ± 0.6 mEq/L [24].

Unlike healthy exercising subjects or normal laboratory animals [19,28], critically ill patients seem to have much higher SIG values [43–48]. Recently, there has been controversy over what constitutes a ''normal'' SIG and whether an abnormal SIG is associated with adverse clinical outcomes. Reports from the United States [43,44,48] and Holland [45] found that the SIG was close to 5 mEq/L in critically ill patients, whereas studies from England and Australia [46,47] found much higher values. The use of resuscitation fluids that contain unmeasured anions (eg, gelatins) could be the explanation, but this has not been established. If exogenous anions are administered, the SIG will be a mixture of endogenous and exogenous anions and, possibly, of different prognostic significance. The two studies that involved patients who received gelatins [46,47] failed to find a correlation between SIG and mortality, whereas studies in patients who did not receive gelatins [43,44,49] found a positive correlation between SIG and hospital mortality. One recent study reported that preresuscitation SIG predicts mortality in injured patients better than blood lactate, pH, or injury severity scores [44]. Dondorp and colleagues [49] had similar results with preresuscitation SIG as a strong mortality predictor in patients who had severe malaria.

The anions that were responsible for the SIG were not identified in any of these studies. Given that individual patients may have SIG values of more than 10 mEq/L to 15 mEq/L, it seems unlikely that any strong ion could be present in the plasma at these concentrations and be unknown to us. Yet, it seems stranger still, for weak acids (eg, proteins) to be the cause given that they are weak. In healthy subjects, the total charge concentration of plasma albumin is only approximately 10 mEq/L to 12 mEq/L. For a similarly charged protein to affect a SIG of 15 mEq/L, it would need to be present in large quantities. The answer, probably, is that the identity of the SIG in these patients is multi-factorial. Endogenous strong ions, such as ketones and sulfate, are added to exogenous ones, such as acetate and citrate. Reduced metabolism of these and other ions as a result of liver [28] and kidney [50] dysfunction likely exacerbates this situation. The release of a myriad of acute phase proteins, principally from the liver, in the setting of critical illness and injury likely adds to the SIG. Furthermore, the systemic inflammatory response is associated with the release of a substantial quantity of proteins, including cytokines and chemokines, some of which, like high-mobility group B1, have been linked to mortality [51]. The cumulative effect of all of these factors may be a reflection of organ injury and dysfunction. It is not surprising that there is a correlation between SIG and mortality. Whatever the source of SIG, it seems that its presence in the circulation, especially early in the course of illness or injury, portends a poor prognosis. Although the prognostic significance of SIG is reduced (or abolished) when exogenous un-

measured anions are administered (eg, gelatins), a SIG acidosis seems to be far worse than a similar amount of hyperchloremic acidosis and more like lactic acidosis in terms of significance [52]. Although it is possible that saline-based resuscitation fluids contaminate the prognostic value of hyperchloremia the same way in which gelatins seem to confound SIG, there remains strong evidence that not all metabolic acidoses are the same.

Summary

Unlike many other areas in clinical medicine, the approach to acid-base physiology often has not distinguished cause from effect. Although it is perfectly reasonable to describe an alteration in acid-base status by the observed changes in H^+ and HCO_3^-, this does not imply causation. The essence of the Stewart approach is the understanding that only three variables are important in determining H^+ concentration: PCO_2, SID, and A_{TOT}. Neither H^+ nor HCO_3^- can change unless one or more of these three variables changes. The principle of conservation of mass makes this point more than semantics. Strong ions cannot be created or destroyed to satisfy electroneutrality, but H^+ ions are generated or consumed by changes in water dissociation. To understand how the body regulates pH we need only ask how it regulates these three independent variables. Other approaches to acid-base physiology ignored the distinction between independent and dependent variables. Although it is possible to describe an acid-base disorder in terms of H^+ or HCO_3^- concentrations or SBE, it is incorrect to analyze the pathology and is potentially dangerous to plan treatment on the basis of altering these variables.

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